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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/764,676	01/26/2004	Peter Rohnert	13183.0037	9441

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EXAMINER	
SOLOLA, TAOFIQ A	
ART UNIT	PAPER NUMBER
1625	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/764,676	ROHNERT ET AL.	
	Examiner	Art Unit	
	Taofiq A. Solola	1625	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on *09 August 2007*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☐ Claim(s) *45-86* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☐ Claim(s) *45-86* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

Claims 45-86 are pending in this application.

Claims 1-44 are cancelled.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 45-86 are rejected under 35 U.S.C. 103(a) as being unpatentable over Jablonka et al., Archivum Vetrinarium Polnicum, (1992), Vol. 32, pages 57-66; in view of Stoll et al., Annals N.Y Accad. Sci. (1994), pages 122-128; Biewenga et al., Gen, Pharm, (1997), Vol. 29(3), pages 315-331; Sian et al., Annals of Neurology, (1994), Vol. 36(3), pg. 348-355; and Kozhevnikova et al., Bull. Experimental Biol. and Med. (1999), Vol. 128(11), pg. 535-537.

Applicant claims a composition comprising ambroxile and Angiotesin-converting enzyme inhibitor (ACE inhibitor) optionally, α-lipoic acid and method of use for treating neurodegenerative diseases. In preferred embodiment applicant claims several dosages, types of composition, and routes of administration.

Determination of the scope and content of the prior art (MPEP 2141.01

Jablonka et al., teach a composition comprising ambroxile for stimulating the production of GSH. Stoll et al., teach a composition comprising α-lipoic acid for improving cognitive function such as, diabetic polyneuropathy, Alzheimer's and Parkinson's diseases and aging. Biewenga et al., teach a composition comprising α-lipoic acid as antioxidants in brain ischemia, stroke, diabetic polyneuropathy, Huntington and Parkinson's diseases. Biewenga et al., also teach that lipoic acid stimulates increased level of GSH in neuroblastoma, melanoma and human T-

lymphocyte cells. Kozhevnikova et al., teach a composition comprising inhibitors ACE inhibitors for neuroprotective activities, e.g. enalapril and captopril in cerebral ischemia.

Sian et al., teach reduced level of GSH in patents suffering from Parkinson's disease and neurodegenerative disorders.

Ascertainment of the difference between the prior art and the claims (MPEP 2141.02)

The difference between the instant invention and that of Jablonka et al., Stoll et al., Biewenga et al., and Kozhevnikova et al., is that applicant claims a composition comprising one or more of ambroxile, ACE inhibitor(s) and α-lipoic acid instead of a composition comprising ambroxile by Jablonka et al., compositions comprising α-lipoic acid by Stoll et al., and Biewenga et al., and a composition comprising enalapril or captopril by Kozhevnikova et al. Applicant also claims several dosages, types of composition, routes of administration and treatment of neurodegenerative disorders.

Finding of prima facie obviousness--rational and motivation (MPEP 2142.2413)

The compositions by the prior arts stimulate GSH level and Sian et al.; teach reduced level of GSH in patents suffering from Parkinson's disease and neurodegenerative disorders. The combination of the prior arts' composition for treating or preventing neurodegenerative disorders is prima facie obvious. "The idea of combining them flows logically from their having been individually taught in the prior art[s]" for stimulating GSH level, and that GSH level is low in neurodegenerative diseases. "Applicant's claim requires no more than mixing together the [individual] compositions." *In re Kerkhoven,* 205 USPQ 1069 (1980). See also, *In re Susi,* 169 USPQ 423, 426 (CCPA, 197). Assuming that compositions comprising ambroxile and Angiotesin-converting enzyme inhibitor (ACE inhibitor) optionally, α-lipoic acid together produce an effect somewhat greater than sum of their separate effects . . . claim to their joint use is not patentable." *In re Crockett,* 126 USPQ 186 (CCPA, 1960). Therefore, the instant invention is

prima facie obvious from the teachings of Jablonka et al., Stoll et al., Biewenga et al., Sian et al., and Kozhevnikova et al. Claiming dosages, types of composition, and routes of administration is not patentable significant because they do not rise to the level of invention under US patent practice. They are obvious modifications available to the preference of an artisan.

Knowing that ambroxile, α-lipoic acid and ACE inhibitors, individually, stimulates GSH level and/or are useful for Parkinson's disease, neurodegenerative disorders and cerebral ischemia, one of ordinary skill in the art would have known to use them individually or combine them in a composition for the diseases. The motivation to combine them is from the teachings of the prior arts and from the common practice in medicine of using cocktail medication.

Objection

Claims 64-81 are duplicates of 45-62 and muse be deleted.

Abstract

The abstract is still too long. Appropriate correction is required.

Drawing

The drawing submitted on 1/26/04 is objected to because hand written inscriptions on each page.

Response to Argument and Affidavit

Applicant's arguments filed 8/9/07 have been fully considered but they are not persuasive. Applicant contends that there must be a teaching, suggestion or motivation in the references to combine them and they must teach all the claimed limitations. This argument is

foreclosed by the decision in *KSR Int. Co. v. Teleflex Inc.,* 127 S.Ct, at 1741, 82 USPQ2d 1385 at 1396 (2007).

Applicant argues that the instant invention is directed to treating "the effects of the total thiol content (i.e. a disturbance of thiol-disulfide status)" not correcting GSH deficiency. This is not persuasive because according to Rossi et al., Biochem. Biophy. Acta, (1995), Vol. 1243, pages 230-238, increased GSH would lead to increased thiol-disulfide molecules particularly protein bound. Applicant also contends that the cited prior arts are directed to free thiol instead of total thiol. This is not persuasive because free thiol must necessarily lead to total thiol, and there is no evidence in the specification or affidavit filed by Tager that this is not true.

Applicant further argues that the Examiner "appears to equate thiol-disulfide with glutathione (GSH)". While applicant admits on record that GSH is oxidized to thiol disulfide, applicant fails to recognize that increased GSH would lead to increased oxidized form. Applicant also argues that when used alone the instant compounds have no effect. This is contrary to the teachings of the prior arts above, and applicant fails to provide conclusive evidence to support this assertion.

Applicant argues that synergistic effect is not expected in the instant case. This is contrary to knowledge well known in the art of medicine in which combinatorial therapy has been practiced for decades in order to obtain synergistic effect. Therefore, the synergist effect obtained in the instant case is a "predictable result". See *KSR,* supra. However, synergistic effect is not enough for unobviousness. "A greater than additive effect is not necessarily sufficient to overcome a prima facie case of obviousness because such an effect can either be expected or unexpected." See MPEP 716.02(a). In the instant case, such additive effect is expected. Further, unobviousness is not overcome where synergistic effect is "[r]eached by means of routine procedures." *Merck & Co. Inc. v. Biocraft Lab. Inc.,* 874 F.2d 804, 10 USPQ2d

1843 (CAFC, 1989). Applicant's claim requires no more than mixing together the compositions" of the prior arts. *In re Kerkhoven,* 205 USPQ 1069 (1980). See also, *In re Susi,* 169 USPQ 423, 426 (CCPA, 197). Such is a routine procedure. Applicant has done no more than combine two separate inventions of prior arts. While the combination may show synergistic effect, it functions no more than what they would have done separately. *In re Anderson,* 396 U.S. 57 (1969) cited in *KSR Int. Co. v. Teleflex Inc*, 550 U.S. ---- (2007), Case No. 04-1350, decided April 30, 2007. A patent for such combination "obviously withdraws what is already known into the field of its monopoly." *Great Atlantic & Pacific Tea Co. v. Supermarket Equipment Corp.,* 340 U.S. 147 (1950), cited in *KSR Int.,* Id. "When a patent simply arranges [combine] old elements with each performing the same function it had been known to perform and yields no more than one would expect from such an arrangement, the combination is obvious. *In re Sakraida,* 425 US 273, 189 USPQ 449 (1976) cited in *KSR, supra.*

It is well known in the art that disulfide thiol is of no use to cells except when in the reduced form (RSH). See the declaration by Dr. Tiger, paragraph 6 (in 10/479,080). However, applicant fails to show conclusive evidence that the instant thiol-disulfide are not reduced and are still useful in the body. Merely showing increased total thiol-disulfide level is not enough.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37

CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Telephone Inquiry

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Taofiq A. Solola, PhD. JD., whose telephone number is (571) 272-0709.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Janet Andres, can be reached on (571) 272-0867. The fax phone number for this Group is (571) 273-8300.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (571) 272-1600.

TAOFIQ SOLOLA
PRIMARY EXAMINER
Group 1625

August 24, 2007